EXHIBIT E

BENNETT ARTICLE

PAIN

The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs

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Abstract

This study describes the development and validation of a novel tool for identifying patients in whom neuropathic mechanisms dominate their pain experience. The Leeds assessment of neuropathic symptoms and signs (LANSS) Pain Scale is based on analysis of sensory description and bedside examination of sensory dysfunction, and provides immediate information in clinical settings. It was developed in two populations of chronic pain patients. In the first ($n = 60$), the use of sensory descriptors and questions were compared in patients with nociceptive and neuropathic pain, combined with an assessment of sensory function. This data was used to derive a seven item pain scale, consisting of grouped sensory description and sensory examination with a simple scoring system. The LANSS Pain Scale was validated in a second group of patients ($n = 40$) by assessing discriminant ability, internal consistency and agreement by independent raters. Clinical and research applications of the LANSS Pain Scale are discussed. Copyright © 2001 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Patients in chronic pain rely on their physicians to identify the pain generating mechanism using clinical information and an understanding of pain classification. Specifically, the clinician must identify whether neuropathic pain generating mechanisms exist in any given patient (defined as pain due to a disturbance of function or pathological change in a nerve (Merskey and Bogduk, 1994)). This is because the successful treatment of neuropathic pain relies on its early identification, an understanding of sustaining mechanisms and the use of alternative therapeutic approaches (Bennett 1994a). Woolf et al. (1998) have recently advanced a more fundamental mechanism-based classification of pain. They propose that pain symptoms, mechanisms and syndromes should form a new hierarchy which does not involve traditional dichotomies such as malignant/non-malignant or acute/chronic. The mechanisms that apply to all body parts should be identified, resulting in two broad pain categories of tissue injury pain or nervous system injury pain, both of which encompass a number of universal mechanisms.

Classically, patients with neuropathic pain complain of

spontaneous pains (those that arise without detectable stimulation) and evoked pains (abnormal responses to stimuli). Spontaneous pains can be continuous, steady and ongoing, or they can be paroxysmal, episodic and intermittent (Tasker, 1984; Wall, 1991; Bennett, 1994b). Evoked pains are often referred to as allodynia, hyperalgesia or hyperpathia. A clinical diagnosis of neuropathic pain should only be made when the distribution of pain and the associated sensory abnormalities jointly, and in a clinical context, point to a neurological condition (Hansson and Kinnman, 1996). Others stress that the most important feature is pain occurring in an area of abnormal or absent sensation (Glynn, 1989). Nerve dysfunction in this context can be represented by sensory, motor or autonomic dysfunction attributable to a discrete neurological lesion (Portenoy, 1992).

Subjective pain experience, particularly sensory pain description, is often used in the identification of neuropathic pain mechanisms, but has rarely been subjected to critical evaluation. Boureau et al. (1990), using a French reconstructed McGill Pain Questionnaire (MPQ), demonstrated significant differences for ten sensory words and seven affective words between patients with peripheral neuropathic and nociceptive pain. The six sensory descriptors more frequently used by neuropathic pain patients were:

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electric shock, burning, cold, pricking, tingling and itching. Masson et al. (1989) discriminated between diabetic neuropathy and other causes of painful diabetic legs using a combination of sensory and affective descriptors, as well as responses to the questions 'when is your pain worse?' and 'what makes your pain worse?'. In contrast, Atkinson et al. (1982), using the standard form MPQ, were unable to discriminate between pain mechanism (e.g. bone, neuropathic or visceral) in a chronic pain population with either benign, cancer or renal pain.

More recently, the Neuropathic Pain Scale (NPS) has been described (Galer and Jensen, 1997) and attempted to discriminate between four diagnostic categories of neuropathic pain using single descriptors. Only post-herpetic neuralgia could be distinguished from the other diagnostic groups (reflex sympathetic dystrophy, diabetic neuropathy and peripheral nerve injury). The NPS was not used to discriminate between neuropathic pain and nociceptive pain symptoms.

To date, a simple clinical tool has not been identified that distinguishes neuropathic symptoms and signs from those arising through nociceptive pain. This study describes the development and validation of a novel tool for identifying patients in whom neuropathic mechanisms dominate their pain experience. The Leeds assessment of neuropathic symptoms and signs (LANSS) Pain Scale is based on analysis of sensory description and bedside examination of sensory dysfunction. More detailed sensory testing, as described by Hansson and Kinnman (1996), was not used as the aim of the study was to develop a diagnostic tool that was easily incorporated into a clinical context.

2. Methods

2.1. Interview setting

This project was undertaken at the Chronic Pain Management Service (CPMS) at St. James's University Hospital, Leeds and involved the development of the pain scale in a group of chronic pain patients (study 1) and its testing in a second group of patients (study 2). Approval for the studies was given by the local research and ethics committee.

The patients were those with chronic pain of any origin, who were able to understand and comply with the requirements of the study which included providing informed consent. The clinical diagnosis was classified by the CPMS clinician as nociceptive or neuropathic pain based on clinical features, known pathology and radiological or electrophysiological evidence. Patients with mixed pain types or where the diagnosis was uncertain were excluded. Patients were interviewed by the author who was blind to the pain classification. The interview consisted of reading out the pain questionnaire under development and asking patients to decide whether the description matched their typical pain character in the preceding week, or not. The

interview was followed by a sensory examination detailed in each study. Data were also collected on pain intensity and frequency over the previous week using four point categorical scales. These were labelled as none, mild, moderate and severe (coded 0, 1, 2, 3) and none, occasional, frequent and continuous (coded 0, 1, 2, 3), respectively. The pain intensity at the time of interview was recorded on a 100 mm VAS.

The data were analyzed using SPSS computer software. Non-parametric tests were used to examine the distribution of sensory descriptions between pain groups, as well as the ratings of pain intensity and frequency. Logistic regression models were built to determine the contribution of sensory and examination items to the discriminant process.

2.2. Scale construction

2.2.1. Study 1

Sensory description was first presented as a series of six symptom groups comprising a question with related descriptors drawn from published expert opinion and patient surveys (Boureau et al., 1990; Bowsher, 1991; Tasker, 1991; Bennett, 1994b; Galer and Jensen, 1997). Questions were used as they were considered a more sensitive technique for obtaining sensory information than descriptors alone. The questions were constructed to reflect the essence of the symptom, and single descriptors were used to illustrate the meaning of the symptom. These six groups represented two types of continuous superficial pain (thermal and dysaesthesia qualities), continuous deep pain, paroxysmal pain, evoked pain and autonomic dysfunction.

Sensory function of the skin overlying the area of pain (the index site) was compared with that at a non-painful control site in each patient. The control site was either a similar area in the contralateral side, or a non-painful area of adjacent skin. The sensory examination assessed the pin-prick threshold (PPT) and presence of allodynia.

The method used for PPTs is based on that described by Chan et al. (1992). A 23 gauge needle is supported in a syringe barrel onto which a series of different weights are applied. For each weight, the needle is brought perpendicularly into contact with the patient's skin several times so that only the mass exerts downward pressure and not the examiner. The weighted needles are applied in an ascending and descending manner over an area of skin of approximately 1 cm^2. The PPT is defined as the lightest weighted needle that consistently elicits a sharp sensation. For this study, 11 weights were used, 0.3, 0.6, 0.9, 1.2, 1.5, 2.0, 2.5, 3.0, 3.6, 4.2 and 5.0 g, which approximated those described by Chan et al. (1992). Although PPTs test only myelinated Aδ-fibres, there is a strong correlation between pin-prick and thermal thresholds (Chan et al., 1992), suggesting that PPT can give comparable information on the function of unmyelinated C-fibres.

Allodynia was judged to be present when pain was elicited by gently stroking a piece of cotton wool over the

index site and when normal sensation was experienced in the control site. Hyperalgesia was judged to be present when pin-prick testing elicited an exaggerated painful response at the index site compared with the control site, that is the patient reported more pain at the index site than the control site. An elevated PPT within a subject was judged to exist when a heavier weight was needed to elicit a sharp sensation at the index site than at the control site. Given the fixed intervals between the weighted needles, the difference in PPT between sites was expressed as one of these intervals. The presence of any combination of the above abnormalities was categorized as sensory dysfunction.

Sixty patients (30 with neuropathic pain) were asked to rate whether the questions and related descriptors described their pain using yes/no responses. Logistic regression modelling was used to identify the best combination of items (descriptive and examination) that could predict for the presence of neuropathic pain. Items were those that were statistically associated with a diagnosis of neuropathic pain and binary codes were used for item selection, with the type of pain as the binary outcome variable. Logistic regression is preferred to discriminant analysis when the data does not meet normality assumptions and the outcome variable is dichotomous (Hosmer and Lemeshow, 1991). A forward conditional method was used to enter variables when examining best-fit models.

The coefficients for each item in resulting models reflected the change in the log odds (or odds ratio) associated with a 1 unit change in that item, for example a change in odds between 'absent' (0) and 'present' (1) for a scale item. The odds ratio is defined as the probability of an event occurring/probability of the event not occurring. Larger coefficients indicate that the item is associated with a larger change in the odds of an event occurring than items with smaller coefficients. However, the contribution of individual items to the outcome depends on the other variables in the model. That is, the coefficients only apply to that item in relation to the other items. Cut points for predicting neuropathic pain were derived from the inspection of optimum positive and negative predictive values.

2.2.2. Study 2

The LANSS Pain Scale consists of two sides of A4 paper and is designed to be administered in an interview format (see Appendix A). The first side of the scale consists of instructions to be read out to the patient asking that they think about how their pain has felt over the past week and to only say yes to a question if it exactly describes their pain. The five description items are presented with corresponding scale scores. On the reverse side of the page are instructions to examiners on assessing sensory dysfunction, specifically testing for presence of allodynia and for altered PPT. These items are marked as present or absent with appropriate scale scores. The assessor is then asked to sum the scale scores and compare them with the cut-off values.

The difference in group scores in study 1 was used to calculate the number of patients required to detect half the original difference in study 2 with a power of 80% and a two-sided α of 0.05. Using this method, a minimum of 17 patients/group were required. Thus, the LANSS Pain Scale was administered to a second group of 40 patients (20/group) to examine the validity and reliability.

The LANSS Pain Scale was completed with the patient independently on two occasions, first with the investigator, and then with the clinician who was blind to the investigator's score. The maximum interval between ratings was 30 min. The total scale scores from both the investigator and clinician were compared with clinical judgement to evaluate the discriminant validity and reliability between raters. Item scores were also examined for the level of agreement between raters and internal consistency.

3. Results

3.1. Scale construction

3.1.1. Study 1

The two groups contained a variety of diagnoses representative of nociceptive and neuropathic pain (Table 1). The groups were similar in their ratings of present pain intensity, past intensity and pain frequency (Table 2).

There were significant differences in sensory examination between the two pain groups (Table 3). Although there were no significant differences in PPTs at control sites and at index sites between the two pain groups, there was a significant mean difference between control and index sites within each group. When patients with hyperalgesia (i.e. lowered PPT) are excluded, there is a significant difference in index site PPT between the two groups. Significantly more patients with neuropathic pain had allodynia, hyperalgesia or a raised PPT at the index site than patients with nociceptive pain. There was a significant association between allodynia and hyperalgesia, such that no patient had hyperalgesia without having allodynia as well ($P = 0.001$). There was no relationship found between either age and PPT at either control or index sites ($r = 0.1$, $P = 0.45$; and $r = -0.27$, $P = 0.84$ respectively, Pearson's correlation), nor between the presence of sensory dysfunction and age when the effect of pain type was controlled ($r = -0.2$, $P = 0.12$).

Five of the six questions were significantly associated with a clinical diagnosis of neuropathic pain and the presence of sensory dysfunction on bedside examination (defined as allodynia and/or altered PPT; Table 4). The question representing continuous deep pain was used equally by both pain groups. Single descriptors that were significantly associated with neuropathic pain are presented in Table 5.

Logistic regression models were examined with questions and descriptors from each symptom complex to identify those with the best discriminant ability. Redundant items

Table 1
Patient diagnoses in study 1

Neuropathic group (n = 30)	Non-malignant (n = 29)	Post-surgical neuropathy	8
		Post-traumatic neuropathy	6
		Lumbar radiculopathy	5
		Complex regional pain syndrome I	3
		Cervical radiculopathy	2
		Peripheral neuropathy	2
		Post-herpetic neuralgia	2
		Phantom limb pain	1
	Malignant (n = 1)	Lumbosacral plexopathy	1
Nociceptive group (n = 30)	Non-malignant (n = 23)	Low back pain	12
		Arthropathies	6
		Visceral pain	2
		Cervical spine pain	1
		Peripheral vascular pain	1
		Repetitive strain injury	1
	Malignant (n = 7)	Visceral pain	4
		Chest wall pain	2
		Bone metastases	1

were defined as those with no significant association with a clinical diagnosis of neuropathic pain, or those that had poor discriminant ability.

Using these criteria, the final items for the LANSS Pain Scale consisted of questions and descriptors based on five symptom groups combined with two examination items. These were rated as a binary response to the presence of allodynia and the presence of altered PPT.

A simple scoring system based on the odds ratios of each item was constructed to provide immediate information at the point of assessment. The odds ratios for sensory description and examination were used to generate the following scale scores (odds ratios in parentheses, see also Table 6): dysaesthesia group = 5 (5.24); autonomic group = 5 (5.91); evoked pain group = 3 (3.14); paroxysmal group = 2 (2.56); thermal group = 1 (1.41); allodynia = 5 (5.51); and altered PPT = 3 (3.68).

The maximum score using this formula was 24, consisting of 16 points from sensory description and eight points

from sensory dysfunction. When applying the scoring formula retrospectively to the data in study 1, the median scores (with quartile deviations in parentheses) are: 17 (14, 21) for the neuropathic pain group and 4 (1, 8) for the nociceptive pain group, $P < 0.001$, a difference of 13 points. There was very good correlation between the score and a diagnosis of neuropathic pain, $r = 0.727$ ($P < 0.001$, Spearman's correlation). A cut-off value of 12 provided the best classification and predictive values (Table 7). This value resulted in a sensitivity of 83% and specificity of 87%. The positive and negative predictive values for the scale were 86 and 84%, respectively.

The four nociceptive patients misclassified as neuropathic all had sensory dysfunction in the area of pain and selected between two and four symptoms. Although four of the five neuropathic patients misclassified as nociceptive had raised PPT, none had allodynia. This group only selected 1–2 symptoms of paroxysmal or thermal quality pain.

Table 2
Patient characteristics in study 1

	Neuropathic pain group (n = 30)	Nociceptive pain group (n = 30)	P value
Mean age (years)	48.1	60.8	0.004
Sex (male)	12	14	0.79
Pain due to malignancy	1	7	0.052
Median VAS at interview (quartile deviation)	49 (29, 78)	51 (25, 65)	0.819
Median VRS pain intensity[a]	2[b]	2	0.855
Median VRS pain frequency[a]	3[c]	2[d]	0.066

[a] Summary measure of pain in the previous week.
[b] Moderate pain.
[c] Continuous pain.
[d] Frequent pain.

Table 3
Sensory function in patients with neuropathic and nociceptive pain in study 1

	Neuropathic pain group ($n = 30$)	Nociceptive pain group ($n = 30$)	P value
Control site threshold (g)[a]	0.45 (0.49)	0.49 (0.35)	0.72
Index site threshold (g)[a]	1.17 (1.47)	0.63 (0.42)	0.06
Difference in thresholds (g)[a]	0.72 (1.26)	0.14 (0.29)	0.015
Index site threshold after excluding patients with hyperalgesia (g)[a]	1.89 (1.72)[b]	0.64 (0.43)[c]	0.01
Sensory dysfunction (n)[d]	29	8	<0.001
Allodynia (n)	19	3	<0.001
Raised PPT (n)	17	8	0.035
Hyperalgesia (n)	14	1	<0.001

[a] Figures represent mean values, with SD values in parentheses.
[b] $n = 16$.
[c] $n = 29$.
[d] Sensory dysfunction was defined as any or all of the following at the index site compared to the control site: a raised PPT, presence of allodynia or hyperalgesia.

3.1.2. Study 2

Forty patients were recruited from the CPMS with a variety of either neuropathic or nociceptive pain (20/group) sufficient to detect a five point difference in group scores (Table 8). There were no significant differences between the two pain groups with respect to age, sex, number of patients with malignancy or ratings of pain intensity or frequency (Table 9).

When the clinical assessment was compared with the investigator's ratings, the LANSS Pain Scale was able to correctly identify 82% (33/40) of patients, representing 85% (17/20) sensitivity and 80% (16/20) specificity. A cut-off score of 12 points or more resulted in a positive predictive value of 81% (17/21) and a negative predictive value of 84% (16/19). There was a significant difference between median LANSS scores for the neuropathic and nociceptive pain groups, 16.5 and 2.5, respectively ($P < 0.001$). Misclassed patients were similar in their item selection to the first sample. Thus, the four nociceptive patients classed as neuropathic had sensory dysfunction (including allodynia) and selected 2–4 symptoms. The three neuropathic patients had raised PPT and selected only 1–2 symptoms from the paroxysmal and thermal groups.

Each scale item was significantly associated with neuro-

Table 4
Descriptors significantly associated with neuropathic pain[a]

Symptom group	Descriptor	Neuropathic pain group ($n = 30$)	Nociceptive pain group ($n = 30$)	P value
Thermal	Hot–burning	18	7	0.003
Dysaesthesia	Cutting–lacerating	11	3	0.013
	Pins and needles	14	3	0.002
	Pricking	12	2	0.003
	Tingling	9	2	0.022
	Tight–stretched	12	5	0.028
	Numb	13	6	0.04
Paroxysmal	Electric shocks	8	2	0.035
	Jumping–bursting	8	0	0.003
	Radiating	10	3	0.033
	Stabbing–shooting	20	11	0.017
Evoked	Bedclothes	15	3	0.001
	Stroking	19	6	<0.001
	Tight clothes	19	3	<0.001
	Cold	13	5	0.039
	Warmth	13	1	<0.001
Autonomic	Sweats	6	1	0.041
	Red–pink	11	0	<0.001
	Puffy–swollen	12	4	0.016
	Mottled	8	0	0.003

[a] Number of patients selecting descriptor by pain type in study 1.

Table 5
Number of patients selecting questions by pain type and presence of sensory dysfunction at index site in study 1

Question	Neuropathic pain group ($n = 30$)	Nociceptive pain group ($n = 30$)	P value	Sensory dysfunction ($n = 37$)	No sensory dysfunction ($n = 23$)	P value
Thermal quality	21	10	0.009	26	5	0.001
Dysaesthesia quality	21	5	<0.001	22	4	0.002
Continuous deep pain	20	20	1	27	13	0.261
Paroxysmal quality	23	12	0.008	28	7	0.004
Evoked pain Quality	25	8	<0.001	28	5	<0.001
Autonomic symptoms	20	6	0.001	23	3	<0.001

pathic pain and the response rates for each pain group reflected the response rates in study 1 (Table 10). Thus, symptoms of dysaesthesia, autonomic dysfunction and signs of allodynia are more discriminatory than symptoms of evoked, paroxysmal and thermal pain.

There was good agreement between the ratings of the investigator and the clinician for LANSS score, classification of pain type and individual items on the scale. Cohen's kappa for overall classification was 0.65 ($P < 0.001$) and the kappa values for scale items were between 0.6 and 0.88 (Table 11). The LANSS scores by investigator and clinician were examined for homogeneity with the Wilcoxon signed rank test. There were no significant differences between the two ($P = 0.664$), indicating that the magnitude of difference between the pairs of scores is small and their distributions are similar. The LANSS Pain Scale demonstrates good internal consistency between items, with Cronbach's alpha of 0.74 confirming the reliability demonstrated in study 1.

4. Discussion

This study demonstrates that the LANSS Pain Scale can distinguish patients with neuropathic pain from those with nociceptive pain with a similar accuracy to that anticipated from a retrospective application of the scale. The small fall in overall classification (from 85 to 82%) was anticipated when applying a retrospectively based formula to a new population. The mean group scores and their dispersion about the median were also similar to those in study 1,

suggesting that the scale is consistently distinguishing similar populations.

Ideal measurement scales demonstrate kappa values of greater than 0.5 and values for Cronbach's alpha between 0.7 and 0.9 (Streiner and Norman, 1989). Thus, the reliability and validity of the LANSS Pain Scale was demonstrated against objective standards. None of the items proved to be redundant (all were significantly associated with neuropathic pain), and the items as a whole were shown to be measuring the same construct.

The development of the LANSS Pain Scale enabled clarification of the relative contributions of neuropathic symptoms to the diagnostic process. In these studies, dysaesthesia symptoms have been the most discriminatory, while paroxysmal and thermal have been the least. This is because dysaesthesia has been a relatively common symptom in neuropathic pain, but relatively rare in nociceptive pain. Paroxysmal symptoms, while still frequently found in neuropathic pain, are also common in nociceptive pain. Interestingly, the relative frequencies of the neuropathic descriptions when presented in symptom groupings are similar to each other. This is in contrast to surveys of other neuropathic patients. In two populations of peripheral neuropathic and central pain (Tasker 1990, 1991), the continuous pain (dysaesthesias and thermal quality) was 2–3 times more common than an intermittent or paroxysmal quality (82–100 vs. 14–44%, respectively depending on syndrome). It is not clear though, how this information was collected, and so comparisons are limited.

The discriminant ability of each symptom was based on the responses by patients to scale items. In clinical practice,

Table 6
Logistic regression models using questions for prediction of neuropathic pain in study 1

Question	Odds ratio	P value	Model statistics		% Sensitivity	% Specificity	% Overall
			Goodness of fit	Model Chi-square			
Thermal	1.41	0.668					
Dysaesthesia	5.24	0.049					
Paroxysmal	2.56	0.247					
Evoked pain	3.15	0.175	70.96	41.92 ($P < 0.001$)	93 (28/30)	83 (25/30)	88 (53/60)
Autonomic	5.91	0.035					
Allodynia	5.51	0.03					
Altered PPT	3.68	0.14					

Table 7
Relation of scores to probability of neuropathic pain including cut-off values at various levels

Scores	Probability	Cut value	% Sensitivity	% Specificity	% Overall classification	Positive predictive value (%)	Negative predictive value (%)
0–2	0.03	≥0	100 (30/30)	0 (0/30)	50 (30/60)	50 (30/60)	50 (30/60)
3–5	0.12	≥3	97 (29/30)	40 (12/30)	68 (41/60)	62 (29/47)	92 (12/13)
6–8	0.16	≥6	93 (28/30)	67 (20/30)	80 (48/60)	74 (28/38)	91 (20/22)
9–11	0.51	≥9	93 (28/30)	77 (23/30)	85 (51/60)	80 (28/35)	92 (23/25)
12–14	0.68	≥12	83 (25/30)	87 (26/30)	85 (51/60)	86 (25/29)	84 (26/31)
15–17	0.81	≥15	73 (22/30)	97 (29/30)	85 (51/60)	96 (22/23)	78 (29/37)
18–20	0.93	≥18	47 (14/30)	97 (29/30)	72 (43/60)	93 (14/15)	64 (29/45)
21–24	0.96	≥21	30 (9/30)	100 (30/30)	65 (39/60)	100 (9/9)	59 (30/51)

it is more usual to wait for the patient to volunteer descriptions of their pain before attempting to clarify their experience. It is possible that the discriminant ability of a descriptor is greater when it is volunteered than when it is merely a positive response to a scale item. This may explain the apparent paradox between the traditional view of 'burning' and 'shooting' being diagnostic for neuropathic pain, and their relatively poor discriminant ability in these studies. Thus, the discriminant ability of these descriptors may depend on the context in which they were obtained. Ultimately, a consistent and systematic approach to the collection of sensory information is the only reliable method of assessing this data.

The LANSS Pain Scale attempts to estimate the probability that neuropathic mechanisms contribute to the chronic pain experience in a given patient. Assessors are therefore instructed that 'if score < 12, then neuropathic mechanisms are unlikely to contribute to the patient's pain' and 'if score ≥ 12, then neuropathic mechanisms are likely to contribute to the patient's pain'.

The clinical diagnoses were broadly representative of the two pain types. However, low back pain and arthropathies were common in the nociceptive group, probably because these were the easiest groups in which to exclude a neuro-

pathic component. The patients recruited to these studies were drawn from a heterogeneous group of chronic pain patients attending a regional referral centre and are likely to be representative of chronic pain patients in other similar services. The samples studied however, were polarized into two distinct diagnostic categories and excluded patients where both nociceptive and neuropathic mechanisms were thought to contribute to the pain experience, in keeping with other similar studies (Boureau et al., 1990; Galer and Jensen, 1997). This served to magnify descriptive and examination differences between the two pain types in order to clearly identify neuropathic features in a prospective population. The ability of the LANSS Pain Scale to identify neuropathic features in patients with mixed pain types was not tested, in part due to the lack of a comparative measure to apportion a value to each pain type in such situations. Clinically, it is impossible to state whether there is a 25, 50 or 75% neuropathic pain contribution in any given patient with a mixed pain diagnosis. This methodology may limit the ability to generalize the results to a typical clinical population.

One difficulty encountered in pain research is defining a gold standard for what are essentially subjective experiences. The clinical diagnosis acts as the only available stan-

Table 8
Patient diagnoses in study 2

Neuropathic group (n = 20)	Non-malignant (n = 19)	Post-surgical neuropathy	6
		Complex regional pain syndrome	4
		Lumbar radiculopathy	3
		Post-traumatic neuropathy	2
		Cervical radiculopathy	1
		Meralgia paraesthetica	1
		Post-herpetic neuralgia	1
		Phantom limb pain	1
	Malignant (n = 1)	Brachial plexopathy	1
Nociceptive group (n = 20)	Non-malignant (n = 16)	Low back pain	6
		Arthropathies	6
		Visceral pain	2
		Facial pain	1
		Loin pain	1
	Malignant (n = 4)	Visceral pain	2
		Bone metastases	1
		Chest wall pain	1

Table 9
Patient characteristics in study 2

	Neuropathic pain group ($n = 20$)	Nociceptive pain group ($n = 20$)	P value
Mean age (years)	52.6	55.2	0.61
Sex (male)	7	6	0.82
Pain due to malignancy (n)	1	4	0.18
Median VAS at interview (quartile deviation)	55 (38, 74)	42 (14, 84)	0.9
Median VRS pain intensity[a]	3	3	0.29
Median VRS pain frequency[a]	3	3	0.71
Median LANSS score (quartile deviation)	16.5 (14, 21)	2.5 (0.5, 5.5)	<0.001

[a] Summary measure of pain in the previous week.

dard against which to compare descriptor use, as there remains no independent, objective method of diagnosing the underlying pain mechanism. Efforts were made to minimize variation in the clinical assessment as much as possible, such as the use of standardized definitions of pain types, brief explanation and demonstrations of interview and examination techniques. In addition, much of the recruitment was carried out using only three consultants as assessors who worked within the same clinical service. These efforts would minimize the potential for a circular argument. The finding that nociceptive patients use 'neuropathic' language and demonstrate sensory dysfunction, combined with the failure of the LANSS scale to identify 15% of neuropathic pain patients, suggest that this pattern is unlikely to be the result of clinicians basing their diagnoses on verbal description, particularly 'classic' descriptors, alone. The influence of verbal description on pain classification is therefore likely to be small.

The finding of sensory dysfunction in the nociceptive group could be explained by incorrect clinical diagnosis, but is also likely to reflect the fact that sensory dysfunction is a recognized association of nociceptive pain (Hansson and Lindblom, 1993). It is interesting to conjecture that there are more similarities than differences between pain types. Perhaps authors such as Wall (1989) and Besson and Chaouch (1987) are right to state that the nociceptive/neuropathic divide is an oversimplification of complex processes. These studies support a more flexible model:

chronic pain with variations in neuropathic expression. Although the size of the groups in study 1 were derived empirically, the finding of distinct sensory description within the neuropathic group suggests that they were of sufficient power to demonstrate large effects in the use of language. Were no differences found, it would have been harder to justify the power of study 1. In study 2, the group sizes were based on the magnitude of the difference between group scores in study 1, and the sample size was powerful enough to demonstrate smaller differences than those found. Elements of sensory testing were used to provide evidence of sensory dysfunction in Aδ-fibres (and indirectly in C-fibres (Chan et al., 1992)) and to compare this with sensory description. More precise methods of assessing C- and Aδ-fibre function include thermal threshold testing, and future evaluation of the LANSS Pain Scale might include comparisons with such methods, or even bedside testing of warm and cold discrimination. This latter technique has not been validated in practice.

The ability to identify neuropathic pain mechanisms should lead to individualized treatment resulting in improved pain control, enable the comparison of treatments in patients with similar pain generating mechanisms and help to tailor the development of new treatments based on specific pain mechanisms. To date, published evidence in support of this is weak. Byas-Smith et al. (1995) reported that six of eight neuropathic pain patients who consistently

Table 10
Number of patients in study 2 selecting scale item by pain type

Item	Neuropathic pain group ($n = 20$)	Nociceptive pain group ($n = 20$)	P value
Dysaesthesia	16	4	<0.001
Autonomic dysfunction	11	2	0.006
Evoked pain	14	6	0.026
Paroxysmal	14	6	0.026
Thermal	14	6	0.026
Allodynia	18	3	<0.001
Altered PPT	19	3	<0.001

Table 11
Level of agreement between investigator and clinician on LANSS scale items

Item	Cohen's kappa	P value
LANSS classification	0.65	<0.001
Dysaesthesia	0.6	<0.001
Autonomic dysfunction	0.88	<0.001
Evoked pain	0.8	<0.001
Paroxysmal	0.65	<0.001
Thermal	0.7	<0.001
Allodynia	0.75	<0.001
Altered PPT	0.64	<0.001

derived benefit from clonidine described sharp and shooting characteristics to their pain. This was in contrast to the 33 other patients studied, in whom only 27% had these characteristics. Max et al. (1992) however, found that the degree of pain relief in patients treated with tricyclic antidepressants was similar regardless of the pain qualities. Research in this area is hampered by the lack of a standardized assessment of the clinical features, and the LANSS Pain Scale might serve to improve qualitative data collection in future therapeutic trials. The use of the LANSS Pain Scale by other investigators will allow a fuller evaluation of its validity in this context.

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Appendix A

THE LANSS PAIN SCALE
Leeds Assessment of Neuropathic Symptoms and Signs

NAME_____   **DATE**_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about <u>how your pain has felt over the last week.</u>
- Please say whether any of the descriptions match your pain exactly.

1) **Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.**

    a)   NO - My pain doesn't really feel like this.................................   (0)

    b)   YES - I get these sensations quite a lot...   (5)

2) **Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.**

    a)   NO - My pain doesn't affect the colour of my skin.....................   (0)

    b)   YES - I've noticed that the pain does make my skin look different from normal ....   (5)

3) **Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.**

    a)   NO - My pain doesn't make my skin abnormally sensitive in that area..........   (0)

    b)   YES - My skin seems abnormally sensitive to touch in that area....................   (3)

4) **Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.**

    a)   NO - My pain doesn't really feel like this ....   (0)

    b)   YES - I get these sensations quite a lot ....   (2)

5) **Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations**

    a)   NO - I don't really get these sensations...   (0)

    b)   YES - I get these sensations quite a lot ....   (1)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO, normal sensation in both areas .... (0)

b) YES, allodynia in painful area only .... (5)

2) ALTERED PIN-PRICK THRESHOLD

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO, equal sensation in both areas .... (0)

b) YES, altered PPT in painful area .... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) ....

If score < 12, neuropathic mechanisms are **unlikely** to be contribution to the patient's pain

If score ≥ 12, neuropathic mechanisms are **likely** to be contributing to the patient's pain